Remarks

In the Office Action, the Examiner noted that claims 1 to 20 are pending in the application (however, please note that claim 7 had already been canceled by way of preliminary amendment of October 12, 2004, and therefore, claims 1-6 and 8-20 are pending in this application); claims 4-7 (this should have been 4-6), 9, 10 and 15-20 are withdrawn from consideration; and that claims 1-3, 8 and 11-14 are rejected. By this amendment, claims 1-3 and 11 have been amended, and claims 5, 6, 9 and 15-17 have been cancelled without prejudice or disclaimer of the subject matter contained therein. Thus, claims 1-4, 8, 10-14 and 18-20 are pending in the application. Also, as requested by the Examiner, a cross-reference to related applications is also provided.

No new subject matter has been inserted through these amendments. All of the amendments are fully supported by the specification. Specifically, claims 1-3 and 11 have been amended to place them in better form for allowance. For instance, preamble of claim 1 has been amended to recite the compound of this invention in singular form and certain of the alternative recitations, "and/or" has been amended to recite more affirmatively either "and" or "or" in all of claims 1-3 and 11. Also, recitation of "salt, solvate or hydrate" of the compound of this invention has been recited in the alternative manner. The Examiner's rejections are respectfully traversed below.

Comments on Election/Restriction – Request for Rejoinder

In making the seven-way restriction imposed in this case final, the Examiner has withdrawn claims 4-6, 9, 10 and 15-20. However, as noted above, claims 5-6, 9 and 15-17 have been canceled without prejudice. Applicants believe for the reasons described below, elected claims 1-3, 8 and 11-14 are in condition for allowance. Therefore, rejoinder of withdrawn claims 4, 10 and 18-20 pursuant to the guidelines set forth in MPEP 821.04 is respectfully requested. Specifically, claim 4 recites a method of preparation of compound of formula (I) of claim 1, thus incorporating all of the

limitations of allowable product claim 1. Similarly, claims 10 and 17-20 recite use of compounds of claims 1-3 and 11 in treating various disease states as recited therein, thus all of which are commensurate in scope to those of allowable product claims 1-3 and 11. Accordingly, rejoinder of claims 4, 10 and 18-20 is respectfully requested.

IDS

The Examiner alleges that the IDS submitted on October 12, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each of the cited foreign patent document and the non-patent literature publications.

As a result, Applicants submit concurrently herewith a new IDS with Form 1449, which lists one foreign patent and three non-patent literature publications along with legible copies of said references. Entry of which in to record is respectfully requested. Also, applicants request the Examiner to return an initialed copy of Form 1449 for Applicants' file.

Objections: Contents of Specification

The Examiner has also noted that cross-reference to related applications is missing as required under 37 CFR 1.78 and MPEP § 201.11.

As already mentioned above, Applicants have provided the missing cross-reference by way of this amendment. Accordingly, withdrawal of objection as to specification is respectfully requested.

Rejection Under 35 U.S.C. § 102(a)

Claims 1-3, 8 and 11-14 stand rejected under 35 U.S.C. 102(a) as being anticipated by Bass et al. (Pharmacology, Biochemistry & Behavior, 74(2002) 31-40).

Please note that the publication date of Bass et al. is December 2002, whereas the instant application claims priority to French Patent Application No. 02/04,567, filed April 11, 2002, and therefore, Bass et al. is not available as a prior art.

However, the Examiner alleges that "Applicants cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15."

In response, Applicants have already submitted on August 31,2007, a certified English translation of the above noted priority application, i.e., French Patent Application No. 02/04,567, filed April 11, 2002, which has made of record as evidenced in PAIR. Nevertheless, a copy of said submission is also enclosed herewith for Examiner's convenience. Accordingly, it is respectfully submitted that Bass et al. is not available as a prior art reference, and therefore, rejection as to claims 1-3, 8 and 11-14 is rendered moot. Thus, withdrawal of rejection as to claims 1-3, 8 and 11-14 is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claim 1 stands rejected under 35 USC 103(a) as being unpatentable over Tilley et al. (US 4,916,145)

Specifically, the Examiner alleges that "Tilley et al. teaches compounds with the structural limitations shown in column 1, lines 7-55. Furthermore, the art exemplifies an adjacent homolog of Applicant's genus, found in columns 41 and 42, example 46."

However, as noted above, claim 1, as amended, does not recite the above noted homolog rendering this rejection moot. Accordingly, withdrawal of rejection as to claim 1 is respectfully requested.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 1-4, 8, 10-14 and 18-20 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

As noted above, Applicants concurrently submit herewith a petition for one-month extension of time to make this response timely. Applicants request the

Commissioner to charge these fees and any other fees that are deemed necessary due to this submission to Deposit Account No. **18-1982** for sanofi-aventis U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

December 3, 2007

Respectfully submitted,

Balaram Gupta

Balaram Gupta, Ph. D., J. D.
Registration No. 40,009
Attorney for Applicants

Attachments: A copy of Submission of certified English Translation of French Patent Application No. 02/04,567, filed April 11, 2002

sanofi-aventis U.S. LLC
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626

for Copy

DOCKET NO. SSL0080 USPCT	SERIAL NO. 10/511,040	DATE 8/31/07
APPLICANT(S)/INVENTOR(S) BARTH, et. al.		ATTY B. GUPTA

TITLE OF INVENTION:
Terphenyl Derivatives, Preparation Thereof, Compositions Containing Same

The Patent Office acknowledges and has stamped hereon the date of receipt of the items checked below:

- ☐ Amendment and/or Reply _____
- ☐ Appeal Notice/Appeal Brief
- ☒ Certified Copy FR 0207567
- ☐ Cert. of ~~Exp~~. Mailing, Date: 8/31/07 BG
  No. _____
- ☐ Charge deposit account, in duplicate
- ☐ Demand for PCT examination
- ☐ Extension of time petition
- ☐ IDS (Statement and PTO Form 1449):
  # of pages enc. _____
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- ☐ Fee Transmittal Sheet
- ☐ Patent Application
  _____ Total # of pages (Spec, claims and abstract)
  _____ # of sheets of drawings
  _____ Declaration/Oath: ___ signed ___ unsigned
  _____ Transmittal letter
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- ☐ PCT Application, transmittal, request & fee sheet
- ☐ Petition under 37 CFR _____
- ☐ Power of attorney
- ☐ Reply to Missing Parts/Requirement _____
- ☒ Other FR PRIORITY DOCUMENTS FR 0204567 BG

PTO Date Stamp and Return

BG 9/4/07 fb

ACTION DUE Comments

DUE DATE —

DKTD BY 9-4-07

ATTY BG/Vernon

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Francis Barth, et al.

Examiner: Cho, Jennifer Y.

Group Art Unit.: 1621

Serial No.: **10/511,040**

Filed: **July 11, 2005**

Title: **Terphenyl Derivatives, Preparation Thereof, Compositions Containing Same**

CERTIFICATE OF MAILING (37 CFR 1.8a)

I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450.

Date of Deposit August 31, 2007

Brian Pritchett
(Type or print name of person mailing paper)

(Signature of person mailing paper)

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION AND REQUEST FOR ENTRY OF PRIORITY PAPERS 37 C.F.R. § 1.55(a)

Applicants submit herewith a certified copy of the France application, 0204567, filed on April 11, 2002, along with a certified English translation thereof, which includes a statement that it is a true translation into the English language as required under 37 CFR 1.55 (also see MPEP § 201.15), for which priority is claimed in the above-identified application.

This submission and request for entry is being made to satisfy the requirements under 35 U.S.C. § 119. Please note that no fees are associated with the entry of the priority documents since they are being timely submitted prior to the date the issue fee is due.

Respectfully submitted,

August 31, 2007

Balaram Gupta, Reg. No. 40,009
Attorney/Agent for Applicant

sanofi-aventis U.S. Inc.
U.S. Patent Operations
Route #202-206 / P.O. Box 6800
Bridgewater, New Jersey 08807-0800
Telephone (908) 231-**3364**
Telefax (908) 231-2626

sanofi-aventis Docket No. SSL0080 US PCT

UNITED STATES PATENT AND TRADEMARK OFFICE

I, Charles Edward SITCH BA,

Managing Director of RWS Group Ltd UK Translation Division, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the French and English languages.

3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in France on 11 April 2002 under the number 02/04,567 and the official certificate attached thereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group Ltd

The 23rd day of August 2007

FRENCH REPUBLIC

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INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

PATENT

UTILITY CERTIFICATE – CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director-General of the Institut National de la Propriété Industrielle certifies that the attached document is a true copy of an application for industrial property titleright filed at the Institute.

Drawn up in Paris, 15 NOV. 2004

On behalf of the Director-General of the
Institut National de la Propriété Industrielle
The Patent Department Head

[signature]

Martine PLANCHE

INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE
REGISTERED OFFICE
26 bis, rue de Saint-Petersbourg
75800 PARIS cedex 08
Telephone: 33 (0)1 53 04 53 04
Fax: 33 (0)1 53 04 45 23
www.inpi.fr

1st filing

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INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

26 bis, rue de Saint Pétersbourg
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PATENT
UTILITY CERTIFICATE
Intellectual Property Code - Book VI

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N° 11354*01

REQUEST FOR GRANT 1/2

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Reserved for the INPI

SUBMISSION OF DOCUMENTS
DATE 11 APR. 2002

PLACE 99

NATIONAL REGISTRATION No. ASSIGNED BY THE INPI 02/04,567

DATE OF FILING ASSIGNED BY THE INPI 11 APR. 2002

1 NAME AND ADDRESS OF THE APPLICANT OR THE REPRESENTATIVE TO WHOM THE CORRESPONDENCE IS TO BE ADDRESSED

SANOFI-SYNTHELABO
174, avenue de France
75013 PARIS

Your file references:
(optional) SSL0080/AMS/FR/REX

Confirmation of filing by fax ☐ No. assigned by the INPI to the fax

2 NATURE OF THE APPLICATION	Tick one of the 4 following boxes
Patent application	☒
Utility certificate application	☐
Divisional application	☐
Initial patent application	No. Date / /
or initial utility certificate application	No. Date / /
Conversion of a European patent application *Initial application*	☐ No. Date / /

3 TITLE OF THE INVENTION (200 characters or spaces maximum)

Terphenyl derivatives, preparation thereof, compositions containing same.

4 PRIORITY DECLARATION OR APPLICATION FOR THE BENEFIT OF THE FILING DATE OF A PRIOR FRENCH APPLICATION	
	Country or organisation Date / / No.
	Country or organisation Date / / No.
	Country or organisation Date / / No.
	☐ If there are other priorities, tick the box and use the "continuation" form

5 APPLICANT	☐ If there are other applicants, tick the box and use the "continuation" form
Name or company name	SANOFI-SYNTHELABO
Forenames	
Legal form	S.A.
SIREN No.	. . . . .
APE-NAF Code	. . . .
Address — Street	174, Avenue de France
Address — Postcode and town	75013 | PARIS
Country	FRANCE
Nationality	French
Telephone No. *(optional)*	04 67 10 64 16
Fax No. *(optional)*	04 67 10 68 89
E-mail address *(optional)*	

1st filing

INPI
INSTITUT NATIONAL DE LA PROPRIETE INDUSTRIELLE

PATENT
UTILITY CERTIFICATE

REQUEST FOR GRANT 2/2

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SUBMISSION OF DOCUMENTS
DATE 11 APR. 2002

PLACE 99

NATIONAL REGISTRATION No. ASSIGNED BY THE INPI 02/04,567

DB 540 W / 260899

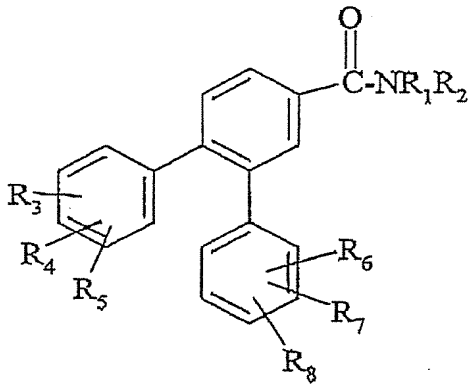
Your file references: *(optional)*	
6 **REPRESENTATIVE** Name Forename Firm or Company No. of permanent power of attorney and/or contractual arrangement Address: Street Address: Postcode and town Telephone No. *(optional)* Fax No. *(optional)* E-mail address *(optional)*	PG.9395
7 **INVENTOR (S)**	
The inventors are the applicants	☐ Yes ☒ No **In this case, provide a separate designation of the inventor(s)**
8 **SEARCH REPORT**	**For a patent application only (including division and conversion)**
Immediate compilation	☒
Deferred compilation	☐
Fee paid in instalments	**Payment in two instalments, for natural persons only** ☐ Yes ☐ No
9 **REDUCTION OF FEES**	**For natural persons only** ☐ Requested for the first time for this invention *(attach notice on non-application)* ☐ Requested prior to filing *(attach copy of favourable decision for this invention or indicate its reference)*
If you used the "continuation" form, give the number of attached pages	

10 **SIGNATURE OF THE APPLICANT OR REPRESENTATIVE (name and capacity of the signatory)** (signature) Anne-Marie SEGRETAIN (PG.9395)	**SIGNED FOR THE PREFECTURE OR THE INPI** (illegible signature)

Law no. 78-17 of 6 January 1978 relating to data processing, files and civil liberties applies to the answers given in this form.
It guarantees right of access to and amendment of data concerning you held at the INPI.

The present invention relates to terphenyl derivatives, to their preparation and to pharmaceutical compositions comprising them.

Accordingly the present invention provides compounds of formula:



(I)

in which:

- R_1 represents a hydrogen atom or a (C_1-C_4)alkyl group;
- R_2 represents a group NR_9R_{10} or a nonaromatic C_3-C_{12} carbocyclic radical which is unsubstituted or substituted one or more times by a methyl group;
- R_3, R_4, R_5, R_6, R_7 and R_8 represent each independently of one another a hydrogen or halogen atom or a (C_1-C_6)alkyl, (C_1-C_6)alkoxy or trifluoromethyl group;
- R_9 and R_{10} together with the nitrogen atom to which they are attached form a saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom selected

from O and N, said radical being unsubstituted or substituted one or more times by a (C_1-C_6)alkyl group;

and their salts, their solvates and their hydrates.

The compounds of formula (I) may exist in the form of bases or of addition salts with acids. These salts are advantageously prepared with pharmaceutically acceptable acids, although the salts of other acids useful, for example, for purifying or isolating compounds of formula (I) also form part of the invention.

A (C_1-C_6)alkyl group is a linear or branched radical such as, in particular: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *tert*-butyl, n-pentyl, isopentyl, n-hexyl or isohexyl, the methyl group being preferred.

A (C_1-C_6)alkoxy group is a linear or branched radical containing 1 to 6 carbon atoms, the methoxy group being preferred.

A halogen atom is a fluorine, chlorine, bromine or iodine atom, fluorine, chlorine or bromine atoms being preferred.

The C_3-C_{12} nonaromatic carbocyclic radicals comprise monocyclic or polycyclic, fused or bridged radicals. The monocyclic radicals include cycloalkyls, for example, cyclopropyl, cyclopentyl, cyclohexyl,

cycloheptyl or cyclooctyl, cyclohexyl and cyclopentyl being preferred. The fused dicyclic or tricyclic radicals, bridged or in spiran form, include for example the radicals norbornyl, bornyl, isobornyl, noradamantyl, adamantyl, spiro[5.5]undecanyl and bicyclo[2.2.1]heptanyl, with spiro[5.5]undecanyl and bicyclo[2.2.1]heptanyl being preferred.

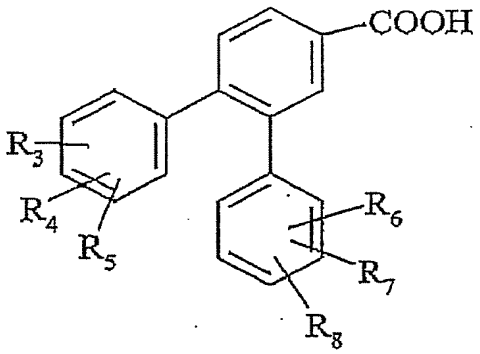
A saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom such as O or N, embraces radicals such as morpholin-4-yl, piperidin-1-yl, piperazin-1-yl, pyrrolidin-1-yl and 3,6-dihydropyridin-1-yl, preference being given to the radicals pyrrolidin-1-yl, piperidin-1-yl and morpholin-4-yl.

Among the compounds provided by the invention mention may be made of the preferred compounds which are defined by the following values for the substituents:

- R_1 represents a hydrogen atom; and/or
- R_2 represents a group selected from piperidin-1-yl, pyrrolidin-1-yl, cyclohexyl, spiro[5.5]undecanyl and 1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl; and/or
- at least one of the substituents R_3, R_4 and R_5 represents a halogen atom or a trifluoromethyl group; and/or

- at least one of the substituents R_6, R_7 and R_8 represents a halogen atom.

The present invention further provides a process for preparing compounds of formula (I). This process is characterized in that a functional derivative of terphenylic acid of formula:



(II)

in which R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for (I) is treated with an amine of formula HNR_1R_2 (III) in which R_1 and R_2 are as defined for (I). Optionally the compound thus obtained is converted into one of its salts and/or solvates.

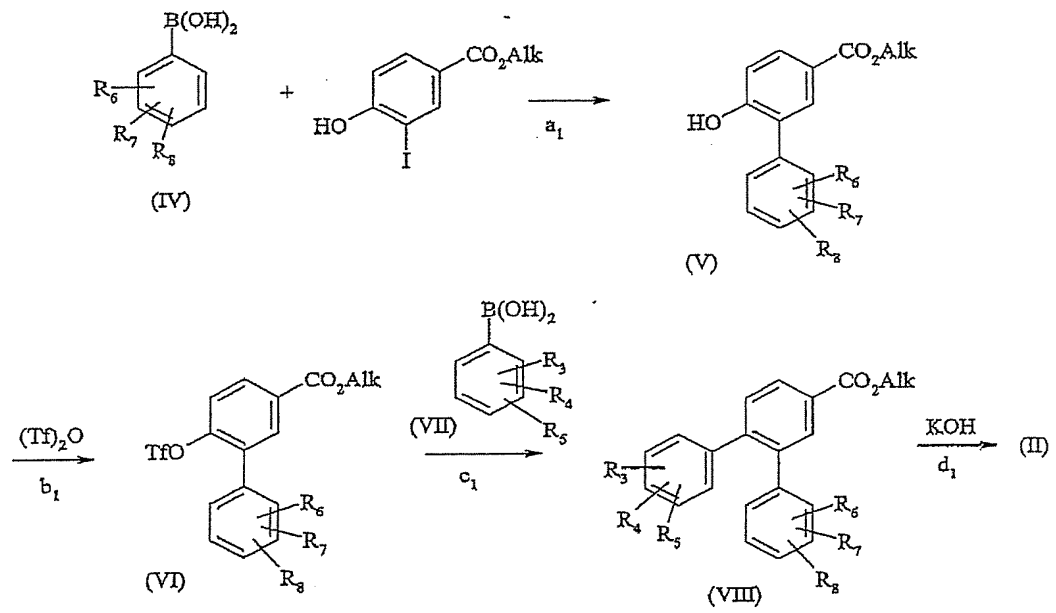
As a functional derivative of the acid (II) it is possible to use the acid chloride, the anhydride, a mixed anhydride, a C_1-C_4 alkyl ester in which the alkyl is linear or branched, an activated ester, for example, the *p*-nitrophenyl ester or the appropriately activated free acid, activated for example with N,N-dicyclohexylcarbodiimide or with benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP).

Thus in the process according to the invention the chloride of pyrazol-3-carboxylic acid, obtained by reacting thionyl chloride with the acid of formula (II), can be reacted with an amine HNR_1R_2 in an inert solvent such as a chlorinated solvent (dichloromethane, dichloroethane, or chloroform, for example), an ether (tetrahydrofuran or dioxane, for example) or an amide (N,N-dimethylformamide, for example) under an inert atmosphere at a temperature of between 0°C and the ambient temperature in the presence of a tertiary amine such as triethylamine, N-methylmorpholine or pyridine.

One variant consists in preparing the mixed anhydride of the acid of formula (II) by reacting ethyl chloroformate with the acid of formula (II) in the presence of a base such as triethylamine and in reacting said mixed anhydride with an amine HNR_1R_2 in a solvent such as dichloromethane under an inert atmosphere at ambient temperature in the presence of a base such as triethylamine.

The acids of formula (II) can be prepared in accordance with the following scheme:

SCHEME 1



Alk = (C_1-C_4)alkyl

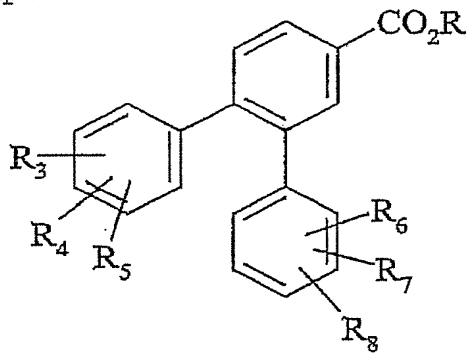
In step a_1 the reaction of the organoborate of formula (IV) with an ester of 4-hydroxy-3-iodobenzoic acid is carried out by the method of Farmaco Ed. Sci., 1958, 13, 121, using the conditions described by Suzuki in Helv. Chem. Acta, 1992, 75, 855.

In step b_1, the product is reacted with triflic anhydride ($(Tf)_2O$) in pyridine in order to prepare the compound of formula (VI). That compound is coupled in step c_1 with an organoborate of formula (VII) under the conditions described in J. Org. Chem., 1992, 57, 379.

The terphenyl ester thus formed is subsequently hydrolyzed by known methods, in the presence of potassium hydroxide, for example, to give

the acid of formula (II).

The acids of formula (II) and their esters of formula (VIII) are new and constitute a final aspect of the invention. Accordingly, the present invention also provides compounds of formula:



(IIbis)

in which R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for (I) and R represents a hydrogen atom or a (C_1-C_4)alkyl group.

The amines HNR_1R_2 (III) are known or are prepared by known methods; by way of example mention may be made of: Chem. Ber. 1986, 119, 1413-1423.

The compounds of the formula (I) possess very good *in vitro* affinity ($IC_{50} \leq 10^{-7}$ M) for cannabinoid receptors CB_1, under the experimental conditions described by M. Rinaldi-Carmona et al. (FEBS Letters, 1994, 350, 240-244).

The antagonist nature of the compounds of formula (I) is demonstrated by the results obtained in adenylate cyclase inhibition models as described in M. Rinaldi-Carmona et al., J. Pharmacol. Exp. Ther.,

1996, 278, 871-878.

The toxicity of the compounds of formula (I) is compatible with their use as a medicinal product.

In accordance with another of its aspects the present invention provides for the use of a compound of formula (I), or of one of its pharmaceutically acceptable salts, solvates or hydrates, for preparing medicinal products intended for treating diseases involving CB_1 cannabinoid receptors.

For example and without limitation, the compounds of formula (I) are useful as psychotropic medicinal products, particularly for treating psychiatric disorders, including anxiety, depression, mood disorders, insomnia, disorders involving delirium, obsessive disorders, psychoses in general, schizophrenia, and also for treating disorders linked to the use of psychotropic substances, particularly in the case of substance abuse and/or substance addiction, including alcohol addiction and nicotine addiction.

The compounds of formula (I) according to the invention can be used as medicinal products for treating migraine, stress, diseases of psychosomatic origin, panic attacks, epilepsy, locomotor disorders, especially dyskinesias or Parkinson's disease, shaking and dystonia.

The compounds of formula (I) according to the

invention can also be used as medicinal products in treating memory disorders, cognitive disorders, especially in treating senile dementia and Alzheimer's disease, and also in the treatment of attention disorders or vigilance disorders. In addition the compounds of formula (I) may be useful as neuroprotective agents, in treating ischemia and cranial traumas and in treating neurodegenerative diseases, including chorea, Huntingdon's chorea and Tourette's syndrome.

The compounds of formula (I) according to the invention may be used as medicinal products in treating pain: neuropathic pain, peripheral acute pain, and chronic pain of inflammatory origin.

The compounds of formula (I) according to the invention may be used as medicinal products in treating appetite disorders, cravings (for sugars, carbohydrates, drugs, alcohols or any appetizing substance) and/or eating disorders, especially as anorexigenic agents or for treating obesity or bulimia, and also for treating type II diabetes or non-insulin-dependent diabetes. Moreover, the compounds of formula (I) according to the invention may be used as medicinal products in treating gastrointestinal disorders, diarrheic disorders, ulcers, vomiting, urinary and bladder disorders, disorders of endocrine origin,

cardiovascular disorders, hypotension, hemorrhagic shock, septic shock, chronic cirrhosis of the liver, asthma, Raynaud's syndrome, glaucoma, fertility disorders, inflammatory phenomena, immune system diseases, especially autoimmune and neuroinflammatory diseases such as rheumatoid arthritis, reactional arthritis, diseases resulting in demyelinization, multiple sclerosis, infectious and viral diseases such as encephalitis, cerebrovascular accidents, and as medicinal products for anticancer chemotherapy and for treating Guillain-Barré syndrome.

According to the present invention the compounds of formula (I) are especially useful for treating psychotic disorders, especially schizophrenia; for treating appetite disorders and obesity; for treating memory and cognitive disorders; for treating alcohol addiction and nicotine addiction, in other words for alcohol withdrawal and tobacco withdrawal.

According to one of its aspects the present invention relates to the use of a compound of the formula (I), of its pharmaceutically acceptable salts and of their solvates or hydrates for treating the disorders and diseases indicated above.

The compound according to the invention is generally administered as a dosage unit.

Said dosage units are preferably formulated

in pharmaceutical compositions in which the active principle is mixed with a pharmaceutical excipient.

Thus, according to another of its aspects, the present invention provides pharmaceutical compositions comprising as active principle a compound of formula (I), one of its pharmaceutically acceptable salts or one of their solvates.

The compound of formula (I) above and the pharmaceutically acceptable solvates or salts thereof can be used at daily doses of from 0.01 to 100 mg per kg of body weight of the mammal to be treated, preferably at daily doses of from 0.02 to 50 mg/kg. In humans the dose can vary preferably from 0.05 to 4000 mg per day, more particularly from 0.1 to 1000 mg per day, depending on the age of the individual to be treated or on the type of treatment, namely prophylactic or curative. Although these doses are examples of average situations, there may be particular cases where higher or lower doses are appropriate, and such doses also belong to the invention. In accordance with usual practice the dose which is appropriate for each patient is determined by the physician according to the method of administration and the age, weight and response of said patient.

In the pharmaceutical compositions of the present invention for oral, sublingual, inhaled,

subcutaneous, intramuscular, intravenous, transdermal, local or rectal administration, the active principle can be administered in unit administration form, as a mixture with conventional pharmaceutical vehicles, to animals and to humans. The suitable unit administration forms comprise oral-route forms such as tablets, gel capsules, powders, granules and oral solutions or suspensions, sublingual and buccal administration forms, aerosols, topical administration forms, implants, subcutaneous, intramuscular, intravenous, intranasal or intraocular administration forms and rectal administration forms.

In the pharmaceutical compositions of the present invention the active principle is generally formulated in dosage units containing from 0.05 to 1000 mg, advantageously from 0.1 to 500 mg, preferably from 1 to 200 mg of said active principle per dosage unit for daily administrations.

In the present description the following abbreviations are used:

DCM: dichloromethane

DMF: dimethylformamide

AcOEt: ethyl acetate

AT: ambient temperature

m.p.: melting point.

For interpreting the nuclear magnetic

resonance (NMR) spectra the following abbreviations are used: s: singlet; d: doublet; m: unresolved multiplet; bs: broad singlet; dd: doublet of a doublet.

Preparation 1.1

(IIa): R_3, R_4, R_5 = 4-Cl; R_6, R_7, R_8 = 2,4-diCl.

Methyl 4-2",4"-trichloro[1,1';2',1"]terphenyl-4'-carboxylate.

A) 4-Hydroxy-3-iodobenzoic acid.

30 g of 4-hydroxybenzoic acid are placed in 780 ml of water containing 18 g of sodium hydroxide, 49.5 g of sodium iodide are added, 675 ml of 3.5% sodium hypochlorite solution are run in slowly and the mixture is left with stirring at AT for 13 hours. 60 ml of concentrated H_2SO_4 are added and then, after cooling, the precipitate formed is filtered off and washed with water. This gives 32.46 g of the expected compound, m.p. = 163°C.

B) Methyl 4-hydroxy-3-iodobenzoate.

32.46 g of the acid obtained in the preceding step is placed in a mixture containing 138 ml of methanol and 10.36 ml of concentrated sulfuric acid and the mixture is heated at reflux for 3 and a half hours. The solvent is concentrated under vacuum and the residue is taken up in demineralized water and ethyl ether. It is neutralized with Na_2CO_3 and then the aqueous phase is extracted with AcOEt. The extract is

washed with water and then with a saturated NaCl solution. This gives 32 g of the expected compound.

C) Methyl 2',4'-dichloro-6-hydroxy-(1,1'-biphenyl)-carboxylate.

5.6 g of methyl 4-hydroxy-3-iodobenzoate are introduced under argon into 50 ml of anhydrous DMF and then 4.2 g of 2,4-dichlorophenylboronic acid and 5.54 ml of triethylamine and then 240 mg of tri-*ortho*tolylphosphine are added and the mixture is left under argon for 1 hour. 180 mg of palladium acetate are added and then the mixture is heated at 100°C for 4 hours. 2 g of 2,4-dichlorophenylboronic acid, 5.54 ml of triethylamine, 120 mg of tri-*ortho*tolylphoshine and 180 mg of palladium acetate are added and then the mixture is heated at 100°C for 8 hours. It is concentrated under vacuum and the residue is taken up in AcOEt and then washed with 10% NH_4OH solution. Extraction is carried out with AcOEt and the extract is washed with water and then with saturated NaCl solution. The residue is dried and then chromatographed on silica, eluting with a cyclohexane/AcOEt mixture (82/18; v/v), to give 3.4 g of the expected compound.

D) Methyl 2',4'-dichloro-6-((trifluoromethyl-sulfonyl)oxy)(1,1'-biphenyl)-3-carboxylate.

3.27 g of the compound obtained in the preceding step are placed in 150 ml of pyridine, the

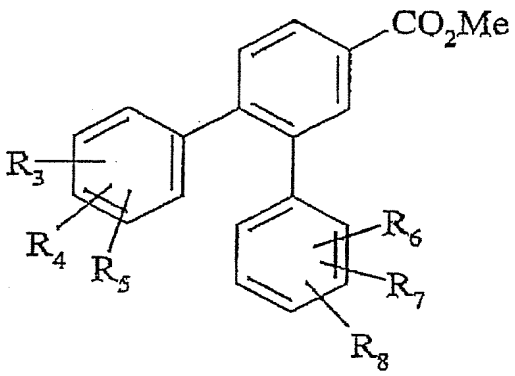
mixture is cooled to between 0°C and 5°C and 2.8 ml of triflic anhydride are run in dropwise. The mixture is maintained with stirring at AT overnight and then concentrated to dryness. The residue is chromatographed on silica, eluting with a cyclohexane/AcOEt mixture (90/10; v/v), to give 3.2 g of the expected compound.

E) Methyl 4,2",4"-trichloro[1,1';2',1"]terphenyl-4'-carboxylate.

3.2 g of the compound obtained in the preceding step are placed in 75 ml of toluene and 2.33 g of 4-chlorophenylboronic acid are added and then 1.55 g of potassium carbonate. The mixture is left under argon for 30 minutes and then 1.38 g of tetrakis(triphenylphosphine)palladium are added and the reaction mixture is heated at between 80°C and 85°C for 3 hours. It is left overnight at AT and then diluted with AcOEt and washed with 5% Na_2CO_3 solution (twice) and then with saturated NaCl solution. It is dried and then the residue is chromatographed on silica with a cyclohexane/AcOEt mixture (80/20; v/v) to give 1.83 g of the expected compound, which crystallizes from isopropyl ether, m.p. = 136°C.

The procedure described above is used to prepare the methyl esters of the acids of formula (II) collated in the table below.

TABLE 1

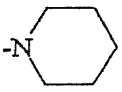


(IIa)

Preparations	R_3, R_4, R_5	R_6, R_7, R_8	m.p.°C/NMR
1.2	4-Cl	4-Cl	223°C
1.3	4-F	2,4-diCl	NMR (DMSO-d_6) δ ppm: 6.9: m: 4H; 7.25: d: 1H; 7.35: dd: 1H; 7.55: m: 2H; 7.80: d: 1H; 8.00: dd: 1H; 13.20: bs: 1H
1.4	4-CF_3	2,4-diCl	206°C

EXAMPLE 1: Compound I

4,2",4"-Trichloro(N-1-piperidinyl)[1,1';2',1"]-terphenyl-4'carboxamide.

(I): R_1 = H; R_2 =  ; R_3, R_4, R_5 = 4-Cl; R_6, R_7, R_8 = 2,4-diCl

A) 4,2",4"-Trichloro[1,1';2',1"]terphenyl-4'-carboxylic acid.

1.33 g of the compound from Preparation 1.1 is suspended in 30 ml of ethanol, 0.95 g of potassium hydroxide in solution in 5 ml of water is added and the mixture is heated at reflux for 2 hours. After cooling

to AT it is filtered over Célite® and concentrated to dryness under vacuum. The residue is taken up in 30 ml of water and then acidified to a pH of 1 by adding 1N HCl. The mixture is cooled using an ice bath and then extracted with AcOEt. It is washed with water and then with saturated NaCl solution to give 1.22 g of the expected compound, m.p. = 237°C.

B) 4,2″,4″-Trichloro[1,1′;2′,1″]terphenyl-4′-carboxylic chloride.

500 mg of the acid obtained in the preceding step are suspended in 50 ml of toluene, 0.3 ml of thionyl chloride is added and the mixture is heated at reflux for 2 hours. The solvent is concentrated twice to give 0.52 g of the expected compound in solid form.

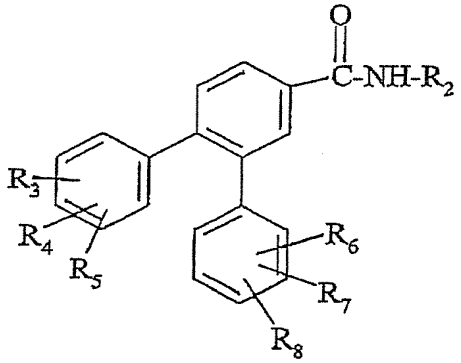
C) 4,2″,4″-Trichloro(N-1-piperidinyl)[1,1′;2′,1″]-terphenyl-4′-carboxamide.

A solution containing 0.17 ml of aminopiperidine and 0.22 ml of triethylamine in 10 ml of DCM is prepared, this solution is cooled to between 0°C and 5°C and 0.52 g of the acid chloride obtained in the preceding step in 10 ml of DCM is added dropwise. The mixture is left at +4°C for 2 days. It is poured into ice-water, then extracted with DCM and washed with 5% Na_2CO_3 solution and then with saturated NaCl solution. The extracts are dried and then the residue is chromatographed on silica, eluting with a

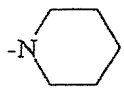
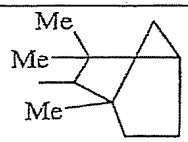
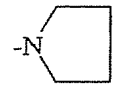
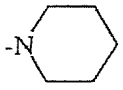
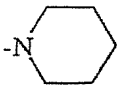
toluene/AcOEt mixture (88/12; v/v). This gives 0.3 g of the expected compound, m.p. = 182°C.

The procedure of Example 1 is used to prepare the compounds of the invention which are described below.

TABLE 2

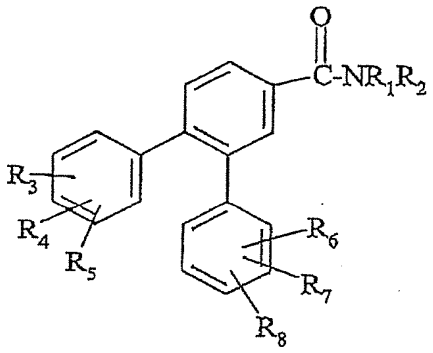


(I)

Examples	R_2	R_3, R_4, R_5	R_6, R_7, R_8	m.p.°c
2		4-Cl	4-Cl	233°C
3	 (1S) endo	4-Cl	2,4-diCl	98°C
4		4-Cl	2,4-diCl	168°C
5		4-F	2,4-diCl	175°C
6		4-CF_3	2,4-diCl	177°C

CLAIMS

1. Compounds of formula:



(I)

in which:

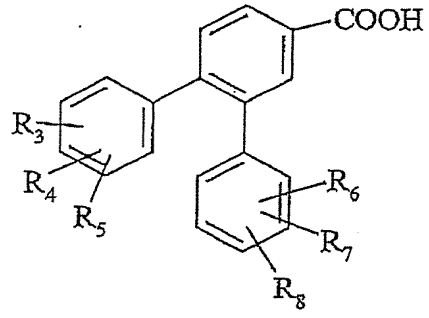
- R_1 represents a hydrogen atom or a (C_1-C_4)alkyl group;
- R_2 represents a group NR_9R_{10} or a nonaromatic C_3-C_{12} carbocyclic radical which is unsubstituted or substituted one or more times by a methyl group;
- R_3, R_4, R_5, R_6, R_7 and R_8 represent each independently of one another a hydrogen or halogen atom or a (C_1-C_6)alkyl, (C_1-C_6)alkoxy or trifluoromethyl group;
- R_9 and R_{10} together with the nitrogen atom to which they are attached form a saturated or unsaturated heterocyclic radical of 5 to 10 atoms, containing or not containing a second heteroatom selected from O and N, said radical being unsubstituted or substituted one or more times by a (C_1-C_4)alkyl group;

and their salts, their solvates and their hydrates.

2. Compounds according to claim 1 of formula (I) in which:

- R_1 represents a hydrogen atom; and/or
- R_2 represents a group selected from piperidin-1-yl, pyrrolidin-1-yl, cyclohexyl, spiro[5.5]undecanyl and 1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl; and/or
- at least one of the substituents R_3, R_4 and R_5 represents a halogen atom or a trifluoromethyl group; and/or
- at least one of the substituents R_6, R_7 and R_8 represents a halogen atom.

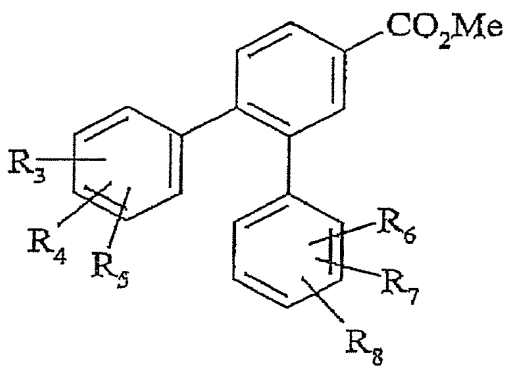
3. A process for preparing a compound of formula (I) according to claim 1 or claim 2, characterized in that a functional derivative of terphenylic acid of formula:



(II)

in which R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for a compound of formula (I) in claim 1 is treated with an amine of formula HNR_1R_2 (III) in which R_1 and R_2 are as defined for a compound of formula (I) in claim 1.

4. Compounds of formula:



(IIa)

in which R_3, R_4, R_5, R_6, R_7 and R_8 are as defined for a compound of formula (I) in claim 1 and R represents a hydrogen atom or a (C_1-C_4)alkyl group.

5. A medicinal product characterized in that it comprises a compound of formula (I) according to either one of claims 1 and 2, or one of its pharmaceutically acceptable salts, hydrates or solvates.

6. A pharmaceutical composition characterized in that it comprises a compound of formula (I) according to either one of claims 1 and 2, or one of its pharmaceutically acceptable salts, hydrates or solvates, and at least one pharmaceutically acceptable excipient.

7. The use of a compound of formula (I) according to either one of claims 1 and 2 for preparing a medicinal product intended for treating any disease involving the CB_1 cannabinoid receptor.